disclosed a method of assessing coronary flow reserve using adenosine injections ranging from 0.05 mg to 0.8 mg.

It is respectfully submitted that the Examiner's assertions are incorrect in that the present invention is not anticipated by Zijlstra.

In order to show anticipation, a single reference must teach (i.e. identically describe) each and every step of the claims. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Applicants submit that the Zijlstra reference does not satisfy this requirement.

Independent claim 22, concerns a method of detecting the presence and assessing the severity of myocardial dysfunction in a human. In contrast, in Zijlstra, it was already determined that the twelve patients being studied had coronary artery disease or myocardial dysfunction. The authors of Zijlstra were only attempting to determine the effect adenosine would have on blood flow through what they knew by other, prior approaches were diseased arteries. Thus, since Zijlstra is not attempting to detect the presence of myocardial dysfunction this reference does not anticipate claim 22. Furthermore, since claims 23, 24, 25, 28, 29, 30, 31, 34, 36 and 37 are dependent on claim 22 they also would not be anticipated by the Zijlstra reference.

With regard to independent claim 58, it concerns a method of determining the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels. In contrast, the authors of the Zijlstra reference were only attempting to determine blood flow through stenotic coronary vessels. Thus, since Zijlstra does not describe determining the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels as stated in claim 58, this reference cannot anticipate independent claim 58 or the claims dependent thereon.

In addition, independent claim 68 is not anticipated by the Zijlstra reference. This claim concerns a method of

determining the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human by administering to said human by intracoronary bolus injection about 2 mcg to about 20 mcg of adenosine and thereafter measuring the difference between flow through these two types of vessels. In contrast, as stated previously, Zijlstra concerns measuring blood flow through only stenotic vessels. Furthermore, Zijlstra administers an intracoronary dose of 0.05 mg to 0.8 mg of adenosine to the patients being studied. This dose is significantly higher than about 2 mcg to about 20 mcg (0.002 mg to 0.02 mg) of intracoronary adenosine administered to humans in the methods of the present invention and specifically claimed in claim 68. Based on these differences the Zijlstra reference does not anticipate claim 68.

In conclusion, since the Zijlstra reference does not identically describe each step of the rejected claims this reference does not anticipate these claims.

The Examiner has also rejected claims 26, 27, 32, 33, 35, 38-57, 61 and 62 under 35 U.S.C. §103 as being unpatentable over Zijlstra. The Examiner alleges that Zijlstra discloses a method for assessing myocardial dysfunction comprising the use of adenosine and a doppler catheter. The Examiner also states that while Zijlstra does not disclose the use of intravenous infusion and other types of imaging, they are all conventional methods known in the art. In conclusion, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to image the heart and coronary arteries using adenosine and any of the known imaging techniques.

Applicants respectfully submit that the Examiner's finding of obviousness in view of Zijlstra is incorrect.

With regard to obviousness of the methods of the present invention, there must be some objective teaching in the prior art to modify a reference to obtain applicants' claimed invention. In re Fine, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988).

Both the suggestion and evidence suggesting that the modification would be successful must be found in the prior art and not in the applicants' disclosure. In re O'Farrell, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). Furthermore, if the accepted wisdom in the art leads away from the claimed invention, this is strong evidence of non-obviousness. In re Hedges, 228 U.S.P.Q. 685 (Fed. Cir. 1986). It is clear the Zijlstra reference does not satisfy these criteria.

Zijlstra discloses tests performed in twelve patients to study coronary flow reserve utilizing a Doppler tip balloon catheter and a coronary vasodilator. The coronary vasodilators used were papaverine and adenosine. In addition, the patients being studied were already found to have coronary artery disease by other techniques. These patients were administered incremental bolus injections of intracoronary adenosine in dosages from 0.05 mg to 0.8 mg. Thereafter, the coronary flow reserve was measured in the diseased arteries using a Doppler catheter. Based on the test results the authors made several comments regarding the poor performance of adenosine in humans to measure coronary flow reserve. For example on page 79 the authors state:

> . . . several characteristics of adenosine limit its practical applicability. First, the dose needed to induce maximal hyperemia varies widely from patient to patient and seems unpredictable. This makes adenosine an unsuitable agent for coronary vasodilation if a radiographic technique is used to measure coronary flow reserve. Second, three of our 12 patients developed bradyarrhythmias immediately following adenosine administration in a dose close to that needed to produce adequate hyperemia. Although these bradyarrhythmias were short-lasting, they produced discomfort for the patients and precluded a meaningful interpretation of the coronary-flow-velocity data after this adenosine injection. The bradyarrhythmic effects of intracoronary adenosine are in accordance with its well-known electrophysiologic effects when administered intravenously. (Emphasis added)

In conclusion, the authors state:

> Intracoronary adenosine is a potent and very short-acting vasodilator. However, its clinical applicability is limited by side effects and unpredictability of the dose needed to induce a maximal hyperemic response in the coronary circulation. (Emphasis added)

Based on the disclosure of Zijlstra, it is respectfully submitted that claims 26, 27, 32, 33, 35, 38-57, 61 and 62 as well as the remaining claims in the present application are not obvious over this reference.

Zijlstra discloses the use of incremental bolus injections of intracoronary adenosine in a dosage range of 0.05 mg to 0.8 mg, to measure coronary flow reserve using a Doppler catheter. However, the authors also state that this method would not be effective clinically because of the side effects of adenosine and the unpredictability of the dose needed to induce maximal hyperemic response in the coronary circulation. In contrast, applicants have shown through tests performed in humans, that adenosine can be administered by intracoronary bolus injection in a dosage of about 2 mcg to about 20 mcg to detect the presence and assess the severity of coronary artery disease, ventricular dysfunction and differences in blood flow through disease free coronary vessels and stenotic coronary vessels without the problems encountered in the Zijlstra study. Thus, applicants have gone against the teachings of Zijlstra to develop the novel methods of the present invention. This shows these novel methods would not have been obvious to a person skilled in the art.

Furthermore, Zijlstra does not test to detect the presence and assess the severity of coronary artery disease, or the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels, or ventricular dysfunction. The method disclosed in Zijlstra only concerns detecting coronary flow reserve in stenotic coronary vessels. Zijlstra's use of a Doppler catheter does nothing more than measure flow. It does not assess myocardial dysfunction. This

is particularly true since the dose needed to induce maximal hyperemia varies from patient to patient and is unpredictable. This is in contrast to the novel methods of the present invention which are used to detect the presence and assess the severity of coronary artery disease, ventricular dysfunction and the difference in flow through disease free coronary vessels and stenotic coronary vessels.

The Zijlstra reference also teaches away from administering adenosine by intravenous infusion or using other types of imaging techniques in conjunction with adenosine to detect myocardial dysfunction. More specifically, on page 76, column 2, the authors state that while adenosine produces maximal coronary vasodilation when given intravenously, this route of administration results in profound alterations of heart rate and arterial pressure. Thus, the authors stated that instead they used gradually incremented doses of intracoronary adenosine. In contrast, applicants have shown through tests performed in humans, that adenosine can be administered by intravenous infusion in a dosage of from about 20 mcg/kg/minute to about 200 mcg/kg/minute, preferably about 140 mcg/kg/minute, to detect the presence and assess the severity of myocardial dysfunction.

With regard to other types of imaging techniques, the Zijlstra reference states on page 79, column 1, that adenosine is an unsuitable agent for coronary vasodilation if a radiographic technique is used to measure coronary flow reserve. In contrast, applicants have shown through tests performed in humans, that adenosine can be used in conjunction with other imaging techniques such as radiopharmaceutical myocardial perfusion imaging and ventricular function imaging to detect myocardial dysfunction.

In conclusion, Zijlstra teaches away from utilizing adenosine to even detect coronary flow reserve or, most certainly, myocardial dysfunction. Zijlstra also teaches away from administering adenosine by intravenous infusion or using it

in conjunction with other imaging techniques. Since applicants have gone against the very limited disclosure in Zijlstra by utilizing adenosine in conjunction with techniques useful to detect the presence and assess the severity of myocardial dysfunction, the novel methods of the present invention are not obvious over this reference.

The Examiner's third ground for rejection alleges that claims 22 to 68 are obvious under 35 U.S.C. §103 in view of Strauss et al., "Non-invasive Detection of Subcritical Coronary Arterial Narrowing with a Coronary Vasodilator and Myocardial Perfusion Imaging", American Journal of Cardiology, Vol. 39: pp 403-406 (1977) ("Strauss").

The Examiner alleges that Strauss teaches myocardial perfusion imaging after the administration of ethyl adenosine-5-carboxylate and thallium-201. The Examiner further alleges that Strauss shows adenosine is used to induce differential perfusion between normal coronary beds and those distal to a substantial stenosis, and that myocardial perfusion imaging is used to detect the resultant difference in regional perfusion. With regard to the different types of myocardial perfusion imaging and blood flow velocity measuring, the Examiner alleges that these are well known and conventionally used methods in the art. With respect to the different dosages, the Examiner alleges that the optimal dosage would be found through routine experimentation. Based on the above the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use adenosine as a vasodilator in humans to replace patient exercise stress testing because Strauss suggested its use in humans.

It is respectfully submitted that the Examiner is incorrect in that the present invention is not obvious in view of Strauss.

As stated previously, for a finding of obviousness, there must be some suggestion in the prior art to modify a

reference to obtain applicants' claimed invention and evidence suggesting that the modification would be successful. In re O'Farrell, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). Furthermore, if the accepted wisdom in the art leads away from the claimed invention, this is strong evidence of non-obviousness. In re Hedges, 228 U.S.P.Q. at 685. It is clear that the Strauss reference does not satisfy these criteria.

Strauss discloses experiments performed on anesthetized dogs utilizing ethyl adenosine-5-carboxylate and myocardial perfusion imaging wherein the radiopharmaceutical agent used was thallium-201. The experiments involved snaring a small segment of the anesthetized dog's left circumflex coronary artery, in order to, as the authors allege, create an artificial subcritical coronary stenosis. Thereafter, the anesthetized dogs were administered ethyl adenosine-5-carboxylate intravenously in a bolus dose of 1 mg/kg. Thallium-201 was then administered to the anesthetized dog and myocardial perfusion imaging was performed on the dog in order to determine myocardial blood perfusion. This was done by sacrificing the animal and evaluating tissue samples. The author states that based on this imaging, there was a decrease in tracer concentration in the zone of the left ventricle supplied by the snared left circumflex coronary artery.

The authors of Strauss suggest that the results of their experiments in animals appear to be sound, but that the sensitivity and specificity of their technique remained to be determined in humans under clinical conditions.

There are significant differences between the Strauss reference and the novel methods of the present invention. Strauss discloses performing experiments in anesthetized dogs as opposed to the novel methods of the present invention which are to be carried out in unanesthetized humans. This distinction is important in that adenosine has been reported to have adverse effects when used in dogs and humans. This has discouraged its use in humans in techniques related to those disclosed in the

present application. This is supported by statements made by researchers studying the use of adenosine in humans. For example, in an article by Wilson et al., entitled "Effects of Adenosine on Human Coronary Arterial Circulation",[2] the authors state at page 1596:

> Despite the widespread use of adenosine in animal studies, concern over adenosine-induced hypotension and heart block have hampered its use in humans. In dogs, intravenous doses sufficient to produce maximal coronary dilation also results in a significant fall in systemic arterial blood pressure. In addition, large doses of adenosine increase the refractory period of the sinoatrial and atrioventricular nodes and can result in heart block. A preliminary study using intracoronary adenosine in humans revealed a strikingly high incidence of adenosine-induced conduction block in the atrioventricular node. Id. at 1596. (Emphasis added)

Furthermore, in editorial comments entitled "Adenosine, Renewed Interest in an Old Drug,"[3] the authors Pantely et al. state at page 1854:

> . . . Despite these interesting characteristics, adenosine never achieved clinical usefulness; rather it found a staid, but secure, role over the years as a short-acting vasodilating agent in experimental animals. (Emphasis added)

In addition, the Zijlstra reference cited by the Examiner in the present Office Action teaches away from the use of adenosine in humans for uses related to those disclosed in the present application. (see pages 4 to 7 of the present amendment).

These references all show that people skilled in the art before and after the filing date of the present application did not think adenosine could be utilized in humans for the uses

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[2] Circulation, Vol. 82, No. 5, pp. 1595-1606, (1990). This reference was cited in the Information Disclosure Statement filed on February 9, 1991 for the present application.

[3] Circulation, 82: 1854-1856 (1990). This reference was cited in the Information Disclosure Statement filed on February 9, 1991 for the present application.

related to those disclosed in the present application because of adenosine's unpredictability and adverse effects. Thus, there is no evidence suggesting that adenosine could be used successfully in humans in methods related to the novel methods claimed in the present application. Strauss measured perfusion by cutting open the dog's heart and evaluating the tissue samples. This is not applicable to testing in humans and is not applicants' technique. Strauss does not use or teach applicants' technique. In contrast, applicants have shown by specific examples that by utilizing the novel methods of the present invention adenosine can be administered to humans and that it is safe and effective. In particular, examples 1, 2 and 3 of the present application shows that adenosine can be used safely and effectively in humans to detect the presence and assess the severity of vascular disease. More specifically, applicants have shown that the methods of the present invention are useful in detecting the presence and assessing the severity of coronary artery disease, detecting the presence and assessing the severity of ventricular dysfunction and determining the difference between blood flow through disease free as opposed to stenotic coronary vessels. Thus, applicants' novel methods go against the teaching in the art.

In conclusion, the conventional wisdom in the art taught against using adenosine in humans for uses related to those disclosed in the present application. The above described statements made by researchers which expressed disbelief that the novel methods of the present invention would work in humans indicates that applicants' invention is non-obvious. U.S. v. Adams, 148 U.S.P.Q. 479, 484 (1966). Furthermore, if the art teaches away from the claimed invention this indicates the invention is not obvious. In re Dow Chemical, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Based on the disclosure of Strauss, the novel methods of the present invention are not obvious.

Moreover, data obtained from anesthetized dogs after the administration of adenosine is not predictive of the effects of adenosine administration on unanesthetized humans. This is because there is significant variability with regard to the effects of adenosine administration in different species, and even different members of the same species. In addition, data obtained from anesthetized dogs after adenosine administration is not predictive of the effects of adenosine on unanesthetized humans because of differences in neurohormonal and autoregulatory control, as well as the fact that anesthesia would mask symptomatic complaints and adverse effects in humans.

Furthermore, in Strauss, ethyl adenosine-5-carboxylate was administered to the anesthetized dogs by a bolus injection of 1 mg/kg. This is much greater than the range of about 2 mcg to about 20 mcg of the specified adenosine receptor agonist given by intracoronary bolus injection in the methods of the present invention. Moreover, the present invention includes administering the adenosine receptor agonist by intravenous infusion at a dosage of about 20 mcg/kg/minute to about 200 mcg/kg/minute, preferably about 140 mcg/kg/minute. There is no disclosure or suggestion in Strauss that the ethyl adenosine-5-carboxylate could be administered as an intravenous infusion for the methods disclosed.

In addition, the Strauss reference discloses snaring a small segment of the anesthetized dog's left circumflex coronary artery, in order to, as the authors allege, create an artificial subcritical coronary stenosis. This artificially induced stenosis poorly reflects the complex clinical setting of an atherosclerotic vessel occlusion in which vasomotor tone, neurohormonal regulation, adenosine receptor sensitivity and effector responsiveness may differ substantially. Furthermore, Strauss only studied a fixed artificial lesion of a particular severity in the anesthetized dogs. It is unpredictable and unobvious that these results can be extrapolated to an

unanesthetized human having stenosis' of differing severity. In contrast, the novel methods of the present invention can be used to detect a broad range of clinically important stenosis' of varying severity. In addition, Strauss only studied an artificial stenosis in the left circumflex coronary artery of anesthetized dogs. It is unpredictable and unobvious that these results can be extrapolated to different types of vessels in the heart of an unanesthetized human. In contrast, the novel methods of the present invention can be used to detect stenosis' of varying severity in any coronary vessel. Thus, it is not possible to predict from the animal experiments performed in Strauss, the safety and efficacy of an adenosine receptor agonist such as adenosine in unanesthetized humans having myocardial dysfunction.

There is also additional support for a finding of the non-obviousness of the present invention in view of Strauss. The Strauss reference was published in March, 1977. Between that date and the filing of the present application there are no references of record, and applicants are not aware of any references, which describe or suggest the successful use of the novel methods of the present invention in humans. This gap of more than 10 years between the date of the Strauss reference and the filing of the present application indicates that those skilled in the art did not think it was feasible to use these novel methods in humans. This also indicates the non-obviousness of the claimed invention. Fromson v. Advance Offset Plate, Inc., 225 U.S.P.Q. 26, 32 (Fed. Cir. 1985).

In conclusion, it is respectfully submitted that the novel methods of the present invention are not obvious in view of Strauss.

The Examiner's fourth ground for rejection is that claims 22 to 68 are obvious under 35 U.S.C. §103 in view of Rumberger et al., "Use of Ultrafast Computed Tomography to Quantitate Regional Myocardial Perfusion: A Preliminary Report,"

Journal of the American College of Cardiology, Vol. 9: No. 1, pp. 59-69 (1987) ("Rumberger").

The Examiner alleges that Rumberger discloses the use of computed tomography to image myocardial perfusion employing adenosine as a vasodilator and that adenosine can be administered by either bolus injection or intravenous infusion. With respect to dosages, the Examiner alleges that optimal dosages would be found through routine experimentation. With regard to the different types of analysis, the Examiner alleges they are all well known conventional methods used in the art. In conclusion the Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use adenosine as a vasodilator in assessing for myocardial dysfunction in humans because Rumberger suggests it and animal testing is used to check for safety before use in humans.

It is respectfully submitted that the Examiner is incorrect in that the methods of the present invention are not obvious in view of Rumberger.

Rumberger discloses preliminary experiments performed in anesthetized dogs to quantify regional myocardial perfusion utilizing adenosine, radiolabelled microspheres and rapid acquisition computed axial tomography. The experimental results were determined after sacrificing the animals and evaluating tissue samples. There is no mention that the anesthetized dogs used in this study had coronary artery disease. Furthermore, the authors allege adenosine is used to produce intermediate and maximal coronary vasodilation during the experiments. The authors state they administered intravenous adenosine in a dosage of 0.5 mg and 1.0 mg/kg/minute to provide this coronary vasodilation. The reference states that the ability to non-invasively assess regional myocardial perfusion and flow reserve would significantly aid in the diagnosis and treatment of patients with heart disease and that the method they disclose offers promise for the quantification of regional myocardial

perfusion and myocardial flow reserve in patients. Importantly, the authors immediately point out that "although the preliminary theoretical and experimental studies are encouraging, they have raised a number of questions related to technical, theoretical and practical limitations related to the application of this method to quantification of regional myocardial perfusion in man."

There are significant reasons why this reference would not render obvious the novel methods of the present invention. The Rumberger reference does not state whether the anesthetized dogs used in the experiments had diseased or disease-free coronary vessels even though the authors allege their methods might be able to be used in the diagnosis and treatment of patients with heart disease. The authors only state that the experiments were performed to quantify regional myocardial perfusion. In contrast, the novel methods of the present invention are specifically directed to detecting the presence and assessing the severity of coronary artery disease, ventricular dysfunction or differences in blood flow through disease-free and stenotic coronary vessels. In addition, applicants novel methods are performed in humans, whereas the experiments performed in Rumberger were performed in anesthetized dogs. This is significant in that, as discussed on pages 9 to 11 of the present amendment, experimental results administering adenosine to anesthetized dogs does not mean adenosine can be used safely and effectively in unanesthetized humans in the novel methods of the present invention since administering adenosine to an unanesthetized human may result in side effects that would negate or limit the compounds utility. In addition, Rumberger administered intravenous adenosine to the dogs in dosages of 0.5 mg/kg/minute and 1.0 mg/kg/minute. In contrast, the novel methods of the present invention involve administering intravenous adenosine to humans in dosages from about 20 mcg/kg/minute (0.02 mg/kg/minute) to about 200 mcg/kg/minute (0.2

mg/kg/minute). This dosage is much lower than the dosage being given to dogs in Rumberger.

Furthermore, the Rumberger reference only states that adenosine was administered to the anesthetized dogs in order to provide intermediate and maximum vasodilation. Thus, Rumberger was only using adenosine as a vasodilator to validate the blood flow quantification technique he was utilizing, and not to assist in detecting the presence and assess the severity of myocardial dysfunction. Just because a compound is useful as a vasodilator does not mean the compound would be useful to detect myocardial dysfunction. For example, calcium channel blockers have been shown to be vasodilators, however these compounds have no role in detecting myocardial dysfunction or myocardial imaging. In contrast, adenosine is used in the methods of the present invention to create an imbalance in perfusion between disease-free and stenotic coronary vessels, in order to detect perfusion deficits and to detect the presence and assess the severity of myocardial dysfunction.

With regard to different types of analysis, Rumberger was specifically using ultrafast computer tomography to study myocardial perfusion. The authors also stated that the preliminary study raised a number of questions as to the application of their method in man. Since the authors were unsure whether their method of analysis could be used in man to quantify regional myocardial perfusion, it cannot be said that other methods of analysis would be obvious.

Thus, for the above reasons the novel methods of the present invention are not obvious in view of Rumberger.

The Examiner's fifth ground for rejection alleges that claims 22 to 68 are obvious under 35 U.S.C. §103 in view of Watt et al., "Adenosine Causes Transient Dilation of Coronary Arteries in Man", British Journal of Clinical Pharmacology, 24: pp. 665-668 (1987) ("Watt").

The Examiner alleges that Watt discloses the use of adenosine as a vasodilator in analyzing blood flow in human patients suffering from chest pain. The Examiner also states that Watt discloses the use of a Baim thermodilution catheter to measure blood flow and that the patients treated with the higher dose of adenosine suffered from chest pain and that no other symptoms were reported. Based on this, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use adenosine as a vasodilator in assessing myocardial dysfunction because Watt suggests it could be used to replace atrial pacing to assess "physiological or pharmacological interventions". In addition, the Examiner alleges, that with regard to different types of imaging, they are all well known and conventional in the art. Furthermore, the Examiner alleges that with regard to specific dosages, the optimal dosages would be found through routine experimentation.

It is respectfully submitted that the novel methods of the present invention are not obvious in view of Watt.

Watt discloses tests performed in 10 normal human subjects to determine the effects of adenosine on coronary blood flow and left ventricular function. This study was carried out during the course of routine investigation of chest pain, however the authors give no reason for this chest pain. Importantly, Watt does not indicate that the subjects were experiencing chest pain just before, or at the commencement of testing. In fact, these patients were shown by other tests to have no significant stenosis at coronary arteriography and no other obvious cardiovascular disease. Coronary blood flow measurements were made immediately before and after each of four single-blind bolus injections into the femoral vein of adenosine in doses of 3.5mg, 6.0mg and 8.5mg. All subjects reported awareness of increased depth of ventilation. In addition, 9 out of the 10 subjects experienced transient chest pain on all doses of adenosine administered. This chest pain was severe enough in three of the

patients to lead to omission of the 8.5 mg dose. In conclusion, Watt states that the results of this study provide direct evidence that adenosine increases coronary flow in man. In addition, the authors conclude that their tests allegedly showed that adenosine increases coronary flow in man and that adenosine induced changes in coronary blood flow are transient and might be usefully applied as an alternative to atrial pacing or intravenous dipyridamole. The authors also state that adenosine might be useful where repeated measurements are required to assess "physiological and pharmacological interventions."

It is respectfully submitted that the novel methods of the present invention are not obvious in view of Watt. This reference discloses tests performed in normal subjects who were shown to have no significant stenosis and no other obvious cardiovascular disease. Thus, Watt was not performing his study to detect the presence and assess the severity of myocardial dysfunction since the authors had already determined that it was not present. This is in contrast to the novel methods of the present invention which are specifically directed to detecting the presence and assessing the severity of myocardial dysfunction. Furthermore, the authors of Watt state that they were only performing their study to determine the effect of adenosine on coronary blood flow and left ventricular function. In addition, the only conclusion reached by the authors of Watt was that their study provided direct evidence that adenosine increases coronary flow in man. There is no disclosure regarding whether adenosine would be useful in detecting myocardial dysfunction. As demonstrated previously on page 16 of the present amendment, just because a compound is useful as a vasodilator does not mean the compound would be useful to detect myocardial dysfunction.

In the last paragraph of the Watt reference the authors allege that adenosine-induced changes in coronary blood flow might be useful to assess "physiological or pharmacological

interventions." The authors do not suggest what they mean by "physiological or pharmacological interventions." This vague, hopeful, qualified prophecy is not enough to render the novel methods of the present invention obvious to a person skilled in the art.

Moreover, this reference is specifically directed to detecting coronary flow in normal subjects using a Baim thermodilution catheter. There is no suggestion in Watt that other imaging techniques could be used in conjunction with adenosine or that they could be used to detect other types of myocardial dysfunction.

In conclusion, for the above described reasons, applicants believe that the Watt reference does not render obvious the novel methods of the present invention.

In the present Office Action, the Examiner also states that the prior art made of record and not relied upon is considered pertinent to applicants' disclosure. The Examiner then cites Biaggioni et al., "Cardiovascular Effects of Adenosine Infusion in Man and Their Modulation by Dipyridamole", Life Sciences, Vol. 39: pp. 2229-2236 (1986) ("Biaggioni"). The Examiner alleges this reference discloses that adenosine may be administered in injections or by intravenous infusion (10 to 140 ng/kg/min) in conscious subjects to act as a vasodilator.

Applicants respectfully submit that Biaggioni only discusses the hemodynamic effects of intravenous infusions of adenosine and its affect on sympathetic activity. This reference concludes that adenosine administered by infusion in the range of 60 to 140 μg/kg/minute to healthy conscious human subjects, lowers diastolic blood pressure but raises heart rate, systolic blood pressure and levels of plasma norepinephrine. Since

Biaggioni is only concerned with the sympathetic effects of adenosine, which has no relation to the novel methods of the present invention, applicants do not believe this reference is relevant.

The Examiner has also cited Berne et al., U.S. Patent No. 4,673,563 which issued June 16, 1987 and is entitled "Adenosine In The Treatment of Supraventricular Tachycardia". The Examiner alleges that this reference discloses that adenosine may be safely administered in the treatment of supraventricular tachycardia. The Examiner also alleges that this reference discloses that adenosine-induced transient A-V block, atrial flutter or fibrillation can be unmasked on the body surface EKG recording in order to more clearly diagnose the disorder. Since Berne is concerned with the treatment of supraventricular tachycardia, which has no relation to the novel methods of the present invention, applicants do not believe this reference is relevant.

For the foregoing reasons, applicants respectfully submit that the claims of the present application are in condition for allowance.

Respectfully submitted,

Date: June 3, 1991

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